FDA Executive Summary

Prepared for the
May 21, 2013 meeting of the
Orthopedic and Rehabilitation Devices Panel

Classification Discussion for Nonthermal
Shortwave Diathermy

Table of Contents

Table of Figures

Table of Tables

1. Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), the Food and Drug Administration (FDA) is convening the Orthopedic and Rehabilitation Devices Advisory Panel (the panel) for the purpose of obtaining recommendations regarding Class III uses of shortwave diathermy systems that were subject to orders under Section 515(i).

The purpose of this panel meeting is to discuss and make recommendations regarding the regulatory classification of shortwave diathermy devices intended for the treatment of medical conditions by means other than the generation of deep heat within body tissues [as defined under the classification regulation 21 CFR Section 890.5290(b)], hereinafter referred to as "nonthermal shortwave diathermy (SWD) devices)," to distinguish them from thermal shortwave diathermy devices classified under 21 CFR 890.5290(a). The Panel will also be asked to discuss whether this device type fits the statutory definition for a Class III device.

FDA is holding this panel meeting to obtain input on the risks to health and benefits of nonthermal SWD devices. The Panel will also be asked to discuss and make recommendations regarding a classification strategy for nonthermal SWD devices currently within this classification regulation. The Panel will discuss whether nonthermal SWD devices should remain in Class III or be downclassified to Class I (subject only to General Controls) or Class II (subject to General and Special Controls). If the Panel believes that a lower classification is appropriate for nonthermal SWD devices, the Panel will also be asked to discuss appropriate controls that would be necessary to mitigate the risks to health.

1.1. Background on the Reclassification Process

FDA regulates medical devices and categorizes them into one of three classes (I, II, or III).

1.1.1. <u>Class I</u>

Class I devices are subject to the least regulatory controls. They usually present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. Class I devices are subject only to general controls, which can include requirements to list medical devices that are marketed with FDA, good manufacturing practices (GMPs), prohibitions against adulteration and misbranding, and labeling devices according to FDA regulations. Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments. Most Class I devices are exempt from premarket review requirements and can be marketed without a premarket submission; many Class I devices are also exempt from GMPs.

1.1.2. Class II

Class II devices are those for which general controls alone are insufficient to reasonably assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are also subject to special controls. Special controls may include requirements for specific labeling or performance testing, including clinical. Most Class II devices must obtain marketing clearance through premarket notification submissions [510(k)s]. Examples of Class II devices include transcutaneous electrical nerve stimulation (TENS) devices, powered wheelchairs, infusion pumps, and surgical drapes.

1.1.3. Class III

Class III is the most stringent regulatory category for devices. Class III devices are typically higher risk devices, but also include devices for which insufficient information exists to assure safety and effectiveness solely through general or special controls. All devices that are not substantially equivalent to any existing devices in Class I or II are automatically classified in Class III. Class III devices typically require marketing approval through a premarket approval (PMA) application.

Class III refers to the class of devices for which premarket approval is or will be required in accordance with section 513 of the Food, Drug, and Cosmetic Act (FD&C Act). A device is in Class III if:

- insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance, and

- the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

Medical devices that require 510(k) submissions are required to demonstrate substantial equivalence to a legally marketed device(s) (*as* safe and *as* effective as). Devices that require PMA applications are required to independently demonstrate safety and effectiveness and to demonstrate that the probable benefit to health from the use of the device outweighs any probable risk of injury or illness from such use.

Although most Class III devices require PMA approval, when FDA's medical device regulation program began in 1976, FDA categorized over 170 devices in Class III, but did not require PMA applications. The intent was that this regulation would be temporary and that, over time, FDA would decide to either reclassify those devices into Class I or II, or to sustain the classification in Class III and call for PMA applications. Nonthermal SWD devices are one of these devices; they are categorized in Class III, but may be cleared for market through a 510(k) submission instead of a PMA application. These devices were categorized in Class III because the Panel of 1979 indicated that it was unclear how nonthermal SWD devices achieved their intended use, and insufficient information on these devices existed to assure safety and effectiveness through Class I or II. FDA agreed and formally classified these devices in Class III in 1983.

The present panel meeting is the result of FDA's ongoing 515 Program Initiative to facilitate the final adjudication of the remaining Class III devices that are regulated through the 510(k) program. FDA is required to hold a meeting of a device classification panel prior to finalizing the reclassification of a device type.

1.2. Indications for Use

The indication for use (IFU) statement identifies the condition and patient population for which a device should be appropriately used, and for which the device has demonstrated a reasonable assurance of safety and effectiveness.

Paragraph (a) of 21 CFR 890.5290, which defines a thermal SWD states, "*A shortwave diathermy for use in applying therapeutic deep heat for selected medical conditions is a device that applies to specific areas of the body electromagnetic energy in the radio frequency bands of 13 megahertz to 27.12 megahertz and that is intended to generate deep heat within body tissues for the treatment of selected medical conditions such as relief of pain, muscle spasms, and joint contractures, but not for the treatment of malignancies.*"

21 CFR 890.5290(b) defines nonthermal SWD as "*A shortwave diathermy for all other uses except for the treatment of malignancies is a device that applies to the body electromagnetic energy in the radio frequency bands of 13 megahertz to 27.12 megahertz and that is intended for the treatment of medical conditions by means other than the generation of deep heat within body tissues as described in paragraph (a) of this section*."

There are slight variations in the indications for use of the nonthermal SWD devices that have been found substantially equivalent through the 510(k) process. Out of the ten devices that FDA cleared as nonthermal SWD, nine of them use the following general statement as their indications for use, "**adjunctive use in the palliative treatment of postoperative pain and edema in superficial soft tissue**." There is one nonthermal SWD cleared by FDA that is indicated for a specific use[1] in "the

[1] FDA has identified general principles in determining when a specific indication for use is reasonably included within a general indication for use of a medical device for purposes of determining substantial equivalence. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073945.pdf

treatment of edema following blepharoplasty." **In the United States, nonthermal SWD devices have only been cleared for prescription use.**

Nonthermal SWD devices have been investigated for a variety of uses over the years including, but not limited to, conditions such as plantar fasciitis, wound healing, whiplash injuries, osteoarthritis, neck disorders, ankle sprains, and chronic pain. The public comments also describe a number of different uses. However, the discussion will be limited to the currently cleared indications. All other uses are beyond the scope of this classification proceeding.

1.3. Device Description

Shortwave diathermy devices for therapy use a radiofrequency (RF) signal that is generated by electronic circuitry at one of two frequencies designated by the U.S. Federal Communications Commission (FCC): 27.12 or 13.56 Megahertz (MHz) to induce electrical currents and voltages in body tissues.[2] The radiofrequency signal is delivered to an antenna or applicator that produces electromagnetic fields external to the applicator. Electric and magnetic fields are induced in body tissues by the applicator. The induced flow of the RF electric current in tissue induces heating.

1.3.1. <u>Distinction between Thermal and Nonthermal Shortwave Diathermy</u>

As explained further below, FDA has differentiated two types of SWD devices that have been cleared through the 510(k) process: thermal and nonthermal.

Thermal SWD devices are designed to deliver therapeutic deep heat below the surface of the skin. Therapeutic deep heat is considered as a sustained temperature increase to 41 – 45°C [1] [2], which triggers blood flow to the heated area. Nonthermal SWD devices do not provide therapeutic deep heat and do not intend to demonstrate a sustained temperature increase to at least 41°C within the tissue. Nonthermal SWD devices are claimed to produce their effect in tissue only through means other than therapeutic deep heating.

Shortwave diathermy equipment can be designed to emit either a pulsatile (pulsed) or a continuous wave output and sometimes provides both types of output. Thermal SWD systems provide continuous wave or pulsed output and achieve therapeutic deep heating of tissues as noted above. Nonthermal SWD devices cleared by FDA deliver RF energy only in a pulsatile fashion and do not provide therapeutic deep heat to the tissues as noted above.

[2] It should be noted that the regulation identifies SWD devices with a carrier frequency of 13.56 to 27.12 MHz. However, the FCC restricts the use of SWD to either 13.56 MHz or 27.12 MHz. All nonthermal SWD devices cleared by FDA utilize the 27.12 MHz carrier frequency.

1.3.2. Components

The design and output of SWD units varies among manufacturers; however, there are several similarities within the devices. General system components for SWD are shown in Figure 1 and include the following:

- Radiofrequency (RF) signal generator that produces a continuous voltage (signal)
- Pulse modulator that turns the signal on or off in a repeating pattern
- Amplifier (optional) that increases the power output of the generator
- Control circuitry that manipulates the operating parameters of the system
- Power supply or a battery
- Patient applicator (an antenna or other device)

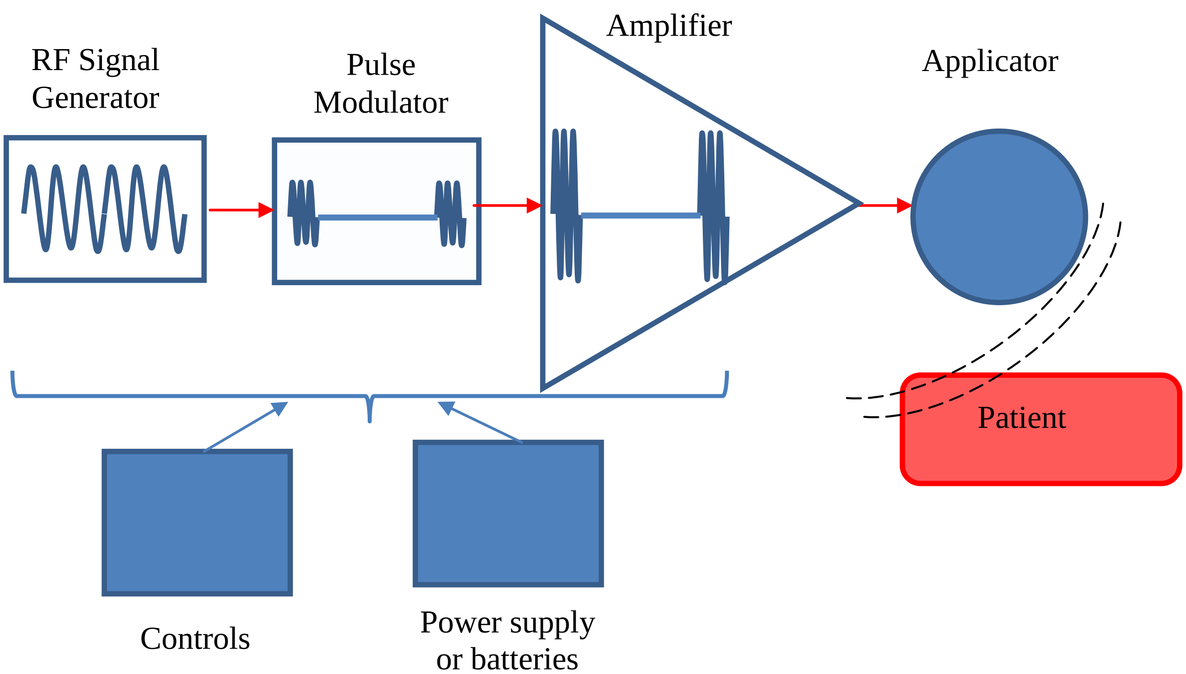

Figure 1 – Components of a shortwave diathermy device

1.3.3. Methods of Application of Electromagnetic Field

The SWD devices apply an electromagnetic field utilizing an inductive (magnetic) applicator and/or a capacitive (electric) applicator. The inductive applicator, which is the most common type, consists of a coil or loop of wire that creates RF magnetic fields when current passes through it. The capacitive applicator consists of a pair of metallic plates or disks placed on opposite sides of the body or an extremity to induce RF electric fields. The same set of components is usually used for both thermal and nonthermal diathermy as discussed in the next section.

1.3.4. Critical parameters for Nonthermal Shortwave Diathermy

Nonthermal SWD devices provide pulsed amplitude modulation, which involves a pulse cycle where RF fields are repeatedly turned on and then off for very brief periods (Figure 2). Pulsed amplitude modulation is characterized by the following parameters:

- Pulse width: the duration of a single RF burst or pulse
- Pulse cycle: the time interval between pulses
- Pulse repetition rate: the number of pulses per second
- Peak power: the maximum amount of power delivered during a pulse cycle.
- Energy density: the amount of energy deposited in a small volume of tissue, averaged over the duration of a single RF pulse (Figure 3).

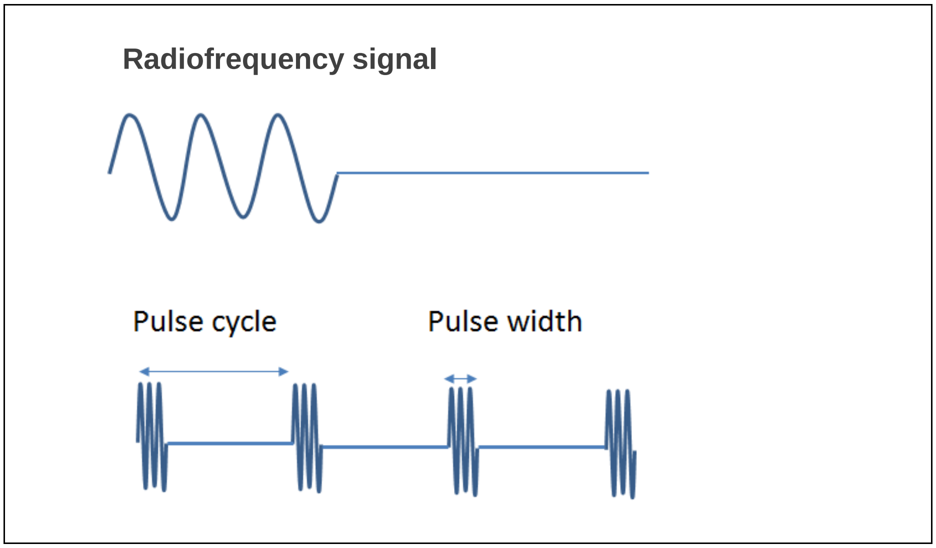

Figure 2 – Pulse amplitude modulation. Pulse cycle and width can vary from microseconds to milliseconds

The output of a SWD device, both thermal and nonthermal, is characterized by the following parameters:

- Power: the rate that RF energy is delivered to the applicator
- Average power: the amount of RF power delivered to the applicator, averaged over the on and off times of the pulse cycle.

The electromagnetic fields from diathermy are characterized by the following parameters:

- External magnetic field strength in air (Amps/meter): a measure of the magnetic field that surrounds a wire carrying a current that varies over time.
- External electric field strength in air (Volts/meter): a measure of the electric field that surrounds an electrically charged object, such as a SWD antenna.
- Internal electric field (Volts/meter): a measure of the electric field in tissues induced by magnetic applicators. The internal fields are non-uniform at any depth with a value of zero at the center of the treated tissues rising to a maximum value at the edge of the tissue under the applicator (Figure 3).

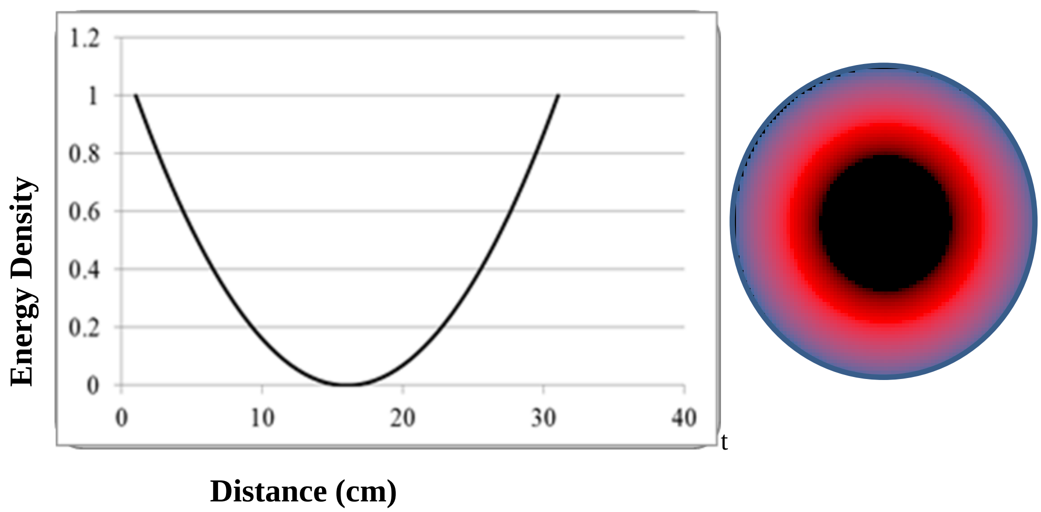

Figure 3 – Internal electric field induced by uniform external magnetic field. 75% of energy density is induced in the outer half of a stationary applicator.

1.3.5. Variability of Nonthermal SWD

Among the different manufacturers, there are substantial differences in output parameters (Table 2). For example, the pulse frequency, pulse duration, and peak power are reported to vary from 2 Hz to 1000 Hz, 60 µs to 2 ms, and 9.8 mW to 975 W, respectively. Also, 75 % of energy density is induced in the outer half of a stationary applicator of some of the devices.

Older models such as the Diapulse device are much bigger in size and deliver higher energy density with higher peak power value. Newer models, such as the Ivivi device, deliver much lower energy density and have a smaller peak power (Figure 4). Therefore, the dose for nonthermal diathermy is extremely variable for the various models and manufacturers and many possible parameters create a great number of combinations of widely differing treatment conditions. It is not clear which parameters and what "dose" (energy density) are considered clinically meaningful, and the papers discussed in Section 6 do not include any information on dose response.

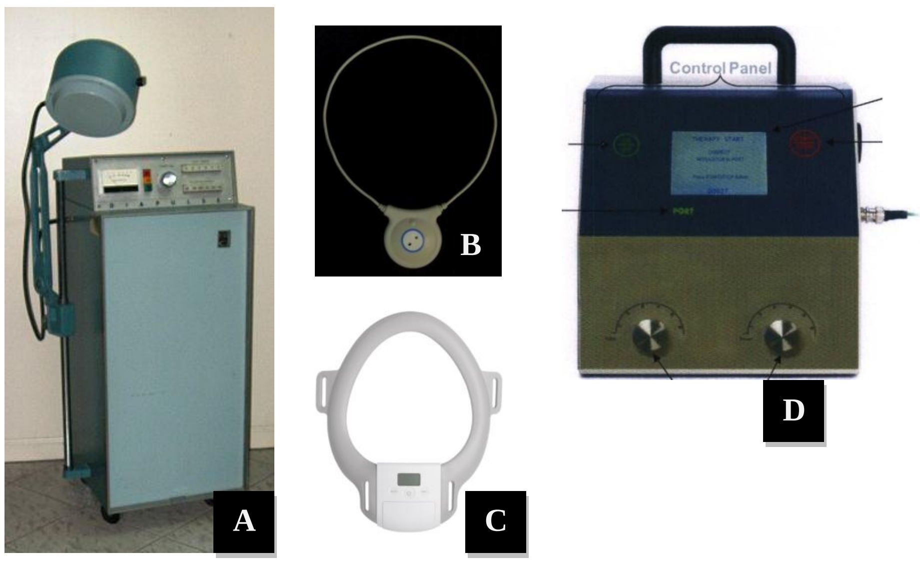

Figure 4 – Pictures of nonthermal SWD devices. (A) Diapulse, (B) Ivivi, Torino (C) Zeobi, (D) Promedtek, Model PMT850

2. Regulatory History

A brief summary of the regulatory history for nonthermal shortwave diathermy devices is provided below.

2.1. Physical Medicine Device Classification Panel Meetings

The Physical Medicine Device Classification Panel, hereinafter referred to as "the Panel," made preliminary classification recommendations for physical medicine devices during a series of meetings. SWD devices were discussed during several different meetings: August 14 and 15, 1975, March 21 and 22, 1976, March 18, 1977, October 14, 1977, and March 17, 1978. The Panel recommended splitting the classification for SWD devices. SWD devices that are "capable of generating therapeutic heat in specific areas of the body" were recommended to be Class II. SWD devices for any use other than delivering therapeutic deep heat, however, were recommended to be Class III. Some of the panel members evaluated the clinical application of the SWD devices and tested the performance of the equipment. It was stated that the therapeutic benefits of diathermy are related to a temperature rise (thermal effect) in the body tissues. The Panel noted that some shortwave devices that used "pulsed radiofrequency outputs" could not provide a sufficient increase in tissue temperature and thus were considered therapeutically ineffective. The Panel found no benefit to utilization of shortwave treatment if the output did not result in a sufficient increase in tissue temperature and recommended that these devices be regulated as Class III devices.

2.2. 1979 Classification Proposed Rules, 1979 Physical Medicine Device Section of the Surgical and Rehabilitation Devices Panel, 1983 Classification Final Rule

Following the classification panel meetings, FDA published a proposed rule on August 28, 1979 (44 FR 50512), classifying nonthermal SWD devices in Class III, to be identified as follows:

> "A shortwave diathermy for any use other than applying therapeutic deep heat is a device that applies the electromagnetic energy of pulsed and/or continuous radiowaves in the radiofrequency bands of 13 megahertz to 27.12 megahertz to the body for any purpose other than applying therapeutic deep heat for the relief of pain."

FDA wrote the following reasons for the recommendation:

- Shortwave diathermy, when it is used for any purpose other than applying therapeutic deep heat, presents a potential unreasonable risk of injury without proven benefit to the patient because substantial data and clinical investigations do not exist to support additional claims made.

- Insufficient information exists to determine that general controls would provide reasonable assurance of the safety and effectiveness of the device when it is used for any purpose other than applying therapeutic deep heat, and that insufficient information exists to establish a performance standard [3] to provide this assurance.

The following were listed as the risks to health:

1. *Cellular or tissue injury:* Nonthermal biological effects of nonionizing radiation may cause cellular or tissue injury.

[3] The original definition of a Class II device in the Medical Device Amendments of 1976 (Pub. L. 94-295) identified performance standards rather than special controls as the mechanism by which FDA could establish reasonable assurance of safety and effectiveness. The Safe Medical Devices Act of 1990 (Pub. L. 101-629) added "special controls," which can include the promulgation of performance standards as well as postmarket surveillance, patient registries, development and dissemination of guidance documents (including guidance for the submission of clinical data in premarket notification submissions), and other appropriate actions as FDA deems necessary to provide such assurance. Section 513(a)(1)(B) of the FDA&C Act.

2. *Pacemaker interference:* The electromagnetic fields generated by the device may interfere with the circuitry of a cardiac pacemaker.

3. *Tissue necrosis (death) and bums:* Excessive energy deposition into the tissue may cause excessive heating that results in tissue damage.

4. *Electrical shock:* Excessive leakage current could result in injury, or a malfunction of the device could result in electrical shock.

When a comment regarding the scope of the identifications for SWD devices in this proposed rule was received, the Agency asked the Physical Medicine Device Section of the Surgical and Rehabilitation Devices Panel (formerly the Physical Medicine Device Classification Panel), hereinafter referred to as "the Physical Medicine Device Section," to review these devices again in December 1979. Among their recommendations, the Physical Medicine Device Section stated that to be therapeutically effective, a SWD device must be capable of providing energy sufficient to raise the temperature of tissues below the skin to 44 °C.

Despite the recommendation of the Physical Medicine Device Section, the Agency did not believe that a reference to therapeutic temperatures such as 44°C was necessary to define deep heat because "the effective therapeutic temperatures for diathermy have been established, and the necessary parameters to assure the effectiveness of diathermy may be addressed in the future in a performance standard."

The final rule classifying SWD devices into a split classification was published on November 23, 1983. The rule revised the information that had been presented in the proposed rule to clarify the distinction between therapeutic deep heat treatment and other modes of action. The rule classified SWD devices into Class II when intended for use in applying therapeutic deep heat for selected medical conditions such as relief of pain, muscle spasms, and joint contractures, but not for malignancies, and Class III for all other uses by means other than the generation of deep heat within body tissue except for the treatment of malignancies. Accordingly, FDA proposed the following split classification regulation under 21 CFR 890.5290:

(a) *Shortwave diathermy* for use in applying therapeutic deep heat for selected medical conditions: (1) Identification. A shortwave diathermy for use in applying therapeutic deep heat for selected medical conditions is a device that applies to specific areas of the body electromagnetic energy in the radio frequency bands of 13 megahertz to 27.12 megahertz and that is intended to generate deep heat within body tissues for the treatment of selected medical conditions such as relief of pain, muscle spasms, and joint contractures, but not for the treatment of malignancies.

(2) *Classification*. Class II (performance standards).

(b) *Shortwave diathermy* for all other uses: (1) Identification. A shortwave diathermy for all other uses except for the treatment of malignancies is a device that applies to the body electromagnetic energy in the radio frequency bands of 13 megahertz to 27.12 megahertz and that is intended for the treatment of medical conditions by means other than the generation of deep heat within body tissues as described in paragraph (a) of this section.

(2) *Classification*. Class III (premarket approval).[4]

In order to require premarket approval, FDA is obligated to issue a notice calling for PMAs and establishing the effective date of that requirement. FDA published a clarification in 1987 that no effective date had been established for the requirement for premarket approval for nonthermal SWD devices (52 FR 17742, May 11, 1987).

Note: Shortwave diathermy devices intended for the treatment of malignancies would be considered postamendments Class III devices, requiring PMAs; these devices are outside the scope of this panel meeting.

2.3. 2009 515(i) Order for Remaining Class III Preamendments Devices

On April 9, 2009, pursuant to Section 515(i) of the FD&C Act, FDA issued an order in the Federal Register [74 FR 16214] to call for information on the remaining Class III 510(k) devices. Included in this group of devices were nonthermal SWD devices, as defined under 21 CFR 890.5290(b). Manufacturers were required to submit a summary of "…information known or otherwise available to them respecting such devices, including adverse safety or effectiveness information concerning the devices…to determine…whether the classification of the device should be revised to require the submission of a PMA…or whether the device should be reclassified into Class I or II."

Letters were sent out to every nonthermal SWD manufacturer registered with FDA, notifying them of this request; each was given until August 7, 2009 to respond. FDA received four submissions from nonthermal SWD manufacturers, and one submission from a manufacturer that does not yet have a marketed nonthermal SWD device. FDA reviewed each submission and used the content to inform its decision how to regulate these devices.

2.4. 2012 Proposed Rule to Require Premarket Approval for Nonthermal SWD Devices

On July 6, 2012, FDA published a proposed rule [77 FR 39953] that would require premarket approval (PMA) for nonthermal SWD devices. In this rule, FDA proposed

[4] It should be noted that ultrasound diathermies (21 CFR 890.5300 (b)) and microwave diathermies (21 CFR 890.5275 (b)) intended to treat medical conditions by means other than generation of deep heat have previously been classified into Class III, requiring PMA.

to require that a PMA application be filed with the Agency for Class III devices within 90 days after issuance of any final rule based on this proposal. An applicant whose device was legally in commercial distribution before May 28, 1976, or whose device had been found to be substantially equivalent to such a device, would be permitted to continue marketing such Class III devices during FDA's review of the PMA.

In the rule, FDA reiterated the concerns of the original classification panels, as well as those identified in the 1979 proposed rule. In addition to the risks to health originally identified by the 1979 Panel, several additional risks to health were included, (a) thermal injury from implanted wire leads and metal implants, (b) radiation hazards, and (c) abnormal cell growth. FDA also performed a literature search for nonthermal SWD studies. FDA focused on studies for the cleared indications for use, and excluded many of the studies from further review because they were conducted on very specific conditions (e.g., wound healing) for which devices have not been explicitly cleared within this classification regulation and are therefore outside the scope. Based on an independent literature review and the review of the responses received from nonthermal SWD manufacturers and others in response to the 515(i) call for information, FDA agreed with the 1979 Panel's findings and concluded, "there is insufficient evidence and information to determine that general controls would provide reasonable assurance of the safety and effectiveness or to establish a performance standard or special controls to provide this assurance."

2.5. Purpose of the Meeting

On July 9, 2012, enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) made changes to Sections 513 and 515 of the FD&C Act. FDASIA changed the process for taking final administrative action for these remaining devices, requiring that FDA use an administrative order process instead of using rulemaking. Under the new requirements, FDA must issue proposed and final orders to call for PMAs for 515(i) devices or reclassify them into class II and hold a device classification panel meeting to consider the classification of each of these devices. FDA would like to request the Panel to comment on whether nonthermal SWD should remain in Class III or be downclassified to Class II with general and special controls.

FDA has conducted additional review of the scientific literature and has carefully reviewed the comments and requests for reclassification received in response to the July 6, 2012, proposed rule.

As previously discussed, devices are Class III if:

- insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance and

- the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

FDA does not believe that nonthermal SWD devices are life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health. However, whether these devices present a potential unreasonable risk of illness or injury is less clear, and previously, FDA recommended Class III for these devices because we determined

a) there *is insufficient information* to determine that general and special controls can provide reasonable assurance of safety and effectiveness, and
b) these devices *present a potential unreasonable risk of injury*.

As discussed in this document, FDA is considering downclassification to Class II for nonthermal SWD devices, with appropriate special controls that we believe should include clinical performance data to demonstrate device effectiveness.

FDA will be requesting Panel feedback regarding whether they believe items (a) and (b), identified immediately above, are still applicable to nonthermal SWD devices.

3. External Stakeholder Responses to FDA's July 6, 2012 Proposed Rule Calling for PMAs

The proposed rule provided for a comment period that was open until October 4, 2012. Responses to the proposed rule included numerous comments, including five comments explicitly submitted to request a change in the classification of nonthermal SWD, as described in Section 3.2 below. The comments as well as redacted versions of the submissions requesting a change in the classification for nonthermal SWD are available at the following address: http://www.regulations.gov/#!docketDetail;D=FDA-2012-N-0378.

3.1. Comments to the Docket [2012-N-0378]

FDA received over 240 comments to the docket, excluding duplicate submissions. Some of the comments have been redacted for public view, either at the request of the submitter or if the comment contained certain types of personal information. If the comments included relevant literature references, these references were checked against the list of references FDA used in their literature review to determine if they had been considered as part of the Agency's assessment.

Comments that expressed an opinion about the classification of nonthermal SWD devices were usually in favor of a Class II designation. Some comments did not openly state an opinion, but included arguments against the proposed rule that could reasonably be interpreted as support for a Class II designation. There were, however, comments from patients and members of the Patient, Consumer, and Public Health Coalition that agreed with a Class III designation. Although the comments report on the effectiveness of nonthermal SWD for a range of conditions and note a general lack of serious adverse events, the evidence is largely anecdotal in nature.

A number of comments were received from a variety of healthcare practitioners. These included plastic and reconstructive surgeons, an orthopedic surgeon, a chiropractor, and a physical medicine and rehabilitation specialist (this is not an all-inclusive list). FDA also received comments from several nonthermal SWD distributors, and employees and shareholders of nonthermal SWD manufacturers. Over 200 of the comments were received from patients who use one specific nonthermal SWD device; there were also several comments from family members of patients. Comments were also received from healthcare practitioners who also use nonthermal SWD devices to treat themselves.

A majority of the indications that were specified, if any were identified, are outside the scope of this proceeding as the devices have not been cleared for the specific indications discussed. Note that the Agency does not regulate the practice of medicine.

3.2. Requests to Change the Classification

FDA received five separate submissions, which were submitted to request a change in the classification of nonthermal SWD from the following entities: BioElectronics Corporation, Diapulse Corporation of America, Leroy Hamilton, Ph.D., MEDIcept, Inc., and Regenesis Biomedical, Inc. The indications for use specified in each submission are not identical and are discussed in Section 3.2.3.

3.2.1. Risks to Health

As noted in Section 2, the 1979 classification Panel identified the following specific risks to health in relation to nonthermal SWD devices:

1. Cellular or tissue injury
2. Pacemaker interference
3. Tissue necrosis (death) and bums
4. Electrical shock

Since the 1975, 1976, 1977, 1977, and 1978 panel meetings, more is known regarding the risk profile of nonthermal SWD devices. In considering risks to health, the FDA has evaluated the available clinical evidence in the published literature; the device related adverse events reported in the FDA Manufacturer and User Facility Device Experience (MAUDE) database; and the risks identified by the manufacturers who responded to the 2009 call for information.

Therefore, in addition to those risks to health identified by the Panel, the proposed rule of July 6, 2012 identified additional risks to health as the following:

1. Thermal injury from implanted wire leads and metal implants
2. Radiation hazards
3. Abnormal cell growth

It should be noted that upon review of responses submitted to request a change in the classification of nonthermal SWD and further FDA discussions, FDA no longer considers stray RF radiation that does not heat as a hazard or risk to health applicable for nonthermal SWD. The Institute of Electrical and Electronics Engineers (IEEE) [3] and International Commission on Non-Ionizing Radiation Protection (ICNIRP) [4] standards define nonionizing electromagnetic (EM) radiation hazards. They state that the rate of energy delivered to a human body in terms of specific absorption rate (SAR) must be less than 2 W/kg for partial body exposures, averaged over 6 minutes. A value of 2 W/kg raises the temperature in muscle tissue approximately 0.2°C in six minutes. Therefore, nonthermal diathermy cannot violate these radiation safety standards if they do not raise tissue temperature.

The submitted requests to change the classification for nonthermal SWD outlined the following additional risks to health that were not originally identified by the Panel or included within the proposed rule that issued on July 6, 2012. It should be noted that the comments provided did not clearly identify whether the additional identified risks are associated with on-label use of the device.

1. Adverse pregnancy outcome
2. Cancer and tumor promotion
3. Skin reactions
4. Pain
5. Bleeding
6. Ineffective treatment
7. Risk to children
8. Feeling chilly and cold in response to treatment
9. Sensation of localized warmth
10. “Pins and needles" sensation
11. Gout attack in patients with pre-existing gout
12. Mild numbness in the area of treatment
13. Abdominal pain
14. Chest wall sensation
15. Headache
16. Malaise

The panel will be asked to discuss the risks to health that have been identified by the FDA and those who submitted comments requesting reclassification, and whether these risks are appropriate, or whether there are additional risks to health that should be considered for nonthermal SWD.

3.2.2. Special Controls

The requests to change classification state that there are adequate special controls to mitigate the risks to health described in Section 3.2.1 above. The following special controls were proposed by the parties identified in Section 3.2.3 below:

1. Adequate instructions for use, including contraindications and warnings about the possibility of unsafe use

2. Compliance with voluntary consensus standards including those for biocompatibility, electrical safety, electromagnetic compatibility and interference, and quality systems

3. Non-clinical performance testing to provide a reasonable assurance of safety and effectiveness with respect to the output waveform and its specifications, such as output power, pulse width, pulse frequency, duty cycle and average output powered measured from the applicator, specific absorption rates, as well as characterization of the electrical and magnetic fields for each RF antenna and RF antenna orientation/position and characterization of the deposited energy density.

4. Submission of animal and clinical testing when a device uses a new waveform or technology that is not well-characterized

The following table was put together based on the information provided in the request for a change in classification from one of the companies that included the following as recommendations for general and special controls to mitigate the identified risks to health:

Table 1 – List of Potential Risks to Health and Proposed Corresponding General and Special Controls

	Labeling	Biocompatibility Testing	Electrical Safety Testing	Electromagnetic Compatibility Testing	Preclinical Analysis and Testing	Clinical Studies	Compliance with QSR	Animal Studies
Cellular or Tissue Injury	x	x	x		x		x	x
Pacemaker interference	x		x	x	x	x	x	x
Tissue necrosis (death) and bums	x		x		x	x	x	x
Electrical shock	x		x	x	x	x	x	x
Thermal injury from implanted wire leads and metal implants	x		x		x	x	x	x
Abnormal cell growth	x	x	x		x		x	x
Adverse pregnancy outcome	x		x		x	x	x	x
Cancer and tumor promotion	x	x	x		x	x	x	x
Skin reactions		x				x	x	x
Pain	x		x		x	x		x
Bleeding	x				x		x	
Ineffective treatment	x		x	x	x	x	x	x
Risks to children	x				x			
Other identified risks	x				x			

In Section 9.3, FDA has further defined the special controls that we believe are necessary to demonstrate a reasonable assurance of safety and effectiveness for all new nonthermal SWD devices.

The panel will be asked to discuss the adequacy of the proposed special controls in providing a reasonable assurance of safety and effectiveness.

3.2.3. Indications for Use

3.2.3.1. Submissions from Leroy Hamilton, Ph.D. and Regenesis Biomedical, Inc.

The requests seeking a change in classification from Class III to Class II submitted by Leroy Hamilton, Ph.D. and Regenesis Biomedical, Inc. address the current indications for use, per the regulation, for the treatment of "medical conditions by means other than the generation of deep heat within body tissues as described in paragraph (a) of this section."

Because these are the indications that are currently specified in the regulation, they will be the primary focus of this summary.

3.2.3.2. Submissions from MEDIcept, Inc. and Diapulse Corporation of America

The requests seeking a change in classification from Class III to II submitted by MEDIcept, Inc. and Diapulse Corporation of America proposed the currently cleared indications for use of "adjunctive use in palliative treatment of postoperative pain and edema in superficial soft tissue" be considered.

Because these are the indications that are currently cleared and specified in the regulation, they will be the primary focus of this summary.

3.2.3.3. Submission from BioElectronics Corporation

The request seeking a change in classification from Class III to II from BioElectronics Corporation propose that all SWD devices are thermal. They are proposing that their devices should be available with an over-the-counter (OTC) designation. Currently, thermal SWD devices are regulated as Class II devices, and have only been cleared for prescription use (product code: IMJ). BioElectronics is specifically interested in the OTC change as well as a change in classification to Class II for their devices for the indications of treatment of "relief of menstrual pain and discomfort and relief of musculoskeletal pain."

The purpose of this meeting is not to determine what qualifies as thermal or nonthermal SWD, nor to recommend whether the existing prescription use devices can appropriately be used as OTC devices. OTC use of nonthermal SWD or thermal SWD has not been classified by FDA. These discussions are not applicable to the overall classification of the SWD device. Furthermore, the indications for use included within this request are outside the currently cleared indications for use; hence, they are beyond the scope of this classification proceeding.

4. Manufacturer and User Facility Device Experience (MAUDE) Database

The MAUDE database is maintained by the Office of Surveillance and Biometrics at FDA. This database contains adverse events and reportable product problems with medical devices. The database was fully implemented in August 1996, and contains individual adverse event reports submitted by manufacturers, user facilities, importers, and voluntary reporters. Medical device manufacturers are required to report known adverse events as part of the general controls that most medical devices are subject to; patients and consumers are also encouraged to voluntarily report adverse events. The reports recapped immediately below are associated with all legally marketed devices.

FDA has received five adverse events reports (4 manufacturer reports and 1 voluntary report) associated with nonthermal SWD devices as of November 15, 2012. Patient problems were reported as squamous cell carcinoma (2), third degree burn (1), secondary pressure ulcer with blisters (1), and electric shock (1). Five reports over a 17-year-span suggest underreporting by the industry. One does need to note the limitations to MDR reporting, including the fact that not all events are captured since this is a voluntary reporting system. There is insufficient information to link these particular adverse events to the device use.

5. Clinical Background

5.1. Conditions

5.1.1. <u>Postoperative Pain</u>

Pain in the immediate postoperative period is common following most surgical procedures. Contributing factors include the nature of the surgery itself, the associated procedures such as postoperative drains and catheters, and the condition underlying the need for the surgery. It is important to treat postoperative pain effectively. Failure to adequately treat pain can lead to numerous medical complications such as reduced mobility leading to venous thromboemboli and/or pneumonia, prolonged hospital stay, and reduced patient satisfaction.

Control of postoperative pain may be accomplished through the use of local techniques such as regional anesthesia, the use of epidural anesthetics and/or opiates. These techniques may limit the adverse effects that are typically seen with systemic analgesics, especially those due to the use of opiates. However, it is common that systemic drugs such as opiates and non-steroidal anti-inflammatory drugs will be used. Although effective, many pharmacologic treatments for pain, especially the use of opiates, are themselves associated with adverse consequences including nausea and vomiting, bowel dysfunction, urinary retention, respiratory depression and sedation, all also potentially leading to a prolonged hospital stay and delayed recovery. With the increasing use of outpatient surgeries, there is a need for methods to control pain that will allow the patient to remain alert and functional.

5.1.2. Postoperative Edema

Edema following surgical procedures is predominantly related to vasodilation, traumatic extravasation of intravascular fluids and proteins and accumulation of products of the inflammatory process. The exact nature and distribution of the edema may be somewhat unique to the specific surgical procedure.

Control of postoperative edema can be important in preventing secondary complications such as compression of neighboring structures and limitation of range of motion leading to prolonged period of recovery and hospitalization. Common measures to control postoperative edema include the use of local cooling, non-steroidal anti-inflammatory drugs, and corticosteroids.

5.2. Measurement of Pain and Edema

5.2.1. Measurement of Pain

Since pain is essentially a subjective phenomenon and dependent on patient reporting, it is important that the method of measurement of pain be a validated instrument. The most commonly used and validated tools for the assessment of pain are the 11 point numeric rating scale of 0 to 10 on which "0" represents no pain at all and "10" represents the worst pain imaginable. The 0-100 visual analog scale (VAS) on which "0 mm" indicates no pain and "100 mm" indicates the worst pain imaginable is also considered a validated scale for the assessment of pain. A simpler non-numeric scale such as the 4-point verbal rating scale (none, mild, moderate, and severe) is not as commonly used but is considered a validated scale. However, this scale is not as sensitive to change due to an effective treatment compared to the 0 – 100 VAS and 0 – 10 numeric rating scale.

In assessing the effectiveness of a treatment for postoperative pain, it is important to address the variability of the pain with time. This timing includes both time since the procedure as well as the relationship of pain to daily activities. Since postoperative pain is likely to improve spontaneously over the first hours to days after the procedure it is important that postoperative pain be assessed regularly and as often as appropriate. Because pain varies greatly over the course of a day, including with activities such as physical therapy or activities of daily living, an assessment of the worst as well as the average pain over time can be important.

For studies of the treatment of acute postoperative pain, the results of individual pain intensity scores are taken frequently over a period of time appropriate to capture the period of clinically relevant pain. The scores are typically integrated over the acute post-procedure period. Examples of the validated scales of this type are the Total Pain Relief or "TOTPAR" score and the Summary of Pain Difference or "SPID" score.

5.2.2. Measurement of Edema

There are no commonly used or validated measures for the assessment of postoperative edema. The distribution of postoperative swelling is usually unique to the procedure and therefore efforts to measure the edema are also unique. For example, edema following procedures involving the knee may include measurement of the circumference of the knee before and after surgery. Such an objective measurement is more challenging following a procedure such as blepharoplasty, where a less objective scale may be necessary. When an objective scale is not feasible, the patient or clinician may provide a subjective comparison of the treated and untreated eyes; for example, visual assessment of percent reduction of eyelid edema, or a Likert-type scale assessing improvement versus worsening of each eye. The measure used should be validated prior to initiating a clinical trial.

5.3. Clinical Trial Design

Clinical trials of treatments for pain and/or edema should address the following key issues:

5.3.1. Overall Design

Prospective, randomized, controlled clinical trials (RCT) are the standard means of generating valid scientific evidence to demonstrate a reasonable assurance of safety and effectiveness. The often rapid resolution of postoperative pain and edema and the subjective nature of pain reporting indicate the need for RCTs for studies of postoperative pain and edema.

Elimination of bias is important in the conduct of well-controlled clinical trials. Given the subjective nature of pain assessments, it is especially important that trials of treatments for pain include a concurrent "placebo" or "sham" comparator. Placebo group responder rates can be high in well controlled trials of treatments for conditions with subjective outcome measures such as depression or pain [5]. The absolute responder rate in the placebo or sham group depends on the endpoint chosen, but can be as high as 50% in studies of pain [6]. In trials of drugs for pain, the use of an inactive but otherwise identical appearing tablet often serves as the comparator. For trials of a device, a sham device should be associated with the same symptoms as the active treatment device, but used at an ineffective "dose." For example, if active treatment is associated with paresthesias or heat, the sham device should also induce the same symptoms, although perhaps for a very short and ineffective period of time. For studies of devices delivering nonthermal short wave diathermy the sham device should have the same appearance as the "active" device, but in fact not deliver effective treatment.

5.3.2. Population Selected

The inclusion and exclusion criteria should be clearly defined and should be designed to select the appropriate target population. For studies of treatment for postoperative pain and/or edema, eligibility criteria should be appropriate to select a uniform population representative of those undergoing the specific procedure for which a benefit is intended.

Given the differences between the various surgical procedures, including the types of tissues injured, postoperative pain is likely to differ somewhat according to the type of procedure being performed. Therefore, the type and effectiveness of treatment may vary with the nature of the surgery. Consequently, demonstration of the effectiveness of a particular treatment following a specific procedure cannot necessarily be generalized to all surgical procedures. This is especially the case when injury to afferent sensory nerves plays a significant role in the postoperative pain, resulting in "neuropathic pain." Treatments that may be effective for pain due to local tissue injury and/or local inflammation are not necessarily effective when there is a major component of neuropathic pain. Therefore, the patient population should be well defined in regards to type of surgical procedure.

5.3.3. Treatment Paradigm

The specific methods of treatment with the investigational device such as treatment regimen, timing, and device settings should be well defined. If additional treatments are allowed, their use should be documented. This includes the use of analgesics and other local treatments for pain or edema. A method for quantitating the use of these treatments should be specified.

5.3.4. Assessments

Pain should be assessed using a validated method such as the use of the pain scales discussed in Section 5.2.1. Assessment of postoperative edema is somewhat more challenging in that the extent and distribution of post-procedural edema is likely to be somewhat unique to the procedure. This will necessitate the use of a measurement tool appropriate to the circumstance. The methods should be clearly defined and validated. In addition, assessors for both pain and edema should be blinded to the subject's treatment assignment.

5.3.5. Analysis

The methods of analysis of results should be pre-specified. For studies of postoperative pain, this should include the methods for analysis of pain intensity. A primary endpoint and analysis of the endpoint should be pre-specified. The pre-treatment baseline for comparison should be clearly defined. Many trials assess the reduction in pain intensity compared to baseline in the active treatment group compared to the concurrent comparator. However, since the clinical relevance of very small changes in pain intensity is unclear, clinical trials of treatments for pain often define individual patient success in terms of a "responder." A "responder" may be defined in such a way as to incorporate generally accepted criteria for a clinically relevant change in pain intensity. For example, a responder may be defined as a subject with a 30% or greater reduction in pain intensity compared to baseline, or using a "minimum efficacy criterion" (MEC), which may be defined for a given trial as the percent of the maximum possible change from baseline.

It is important that clinical trials of treatment for pain include a measure of the clinical relevance of any changes in pain intensity scores [7]. These may include measures of physical or emotional functioning and usually also include a measure of patient or clinician reported global impression of change (PGIC or CGIC) [8].

It is also critical that the use of analgesic medications be systematically collected and analyzed. Since the potency of these medications varies greatly, it is important to account for these differences by either limiting the analgesics allowed or converting their use to a standardized scale based on potency equivalents. It is important to demonstrate that any apparent benefit of a treatment being studied could not be attributed to an increase in the use of analgesic medications. Conversely, a decline in the use of analgesic medications is supportive of a clinically relevant benefit.

5.3.6. Safety

Collection of adverse events should be prospective, systematic, and comprehensive. All adverse events should be collected and reported regardless of their possible relationship to the investigational treatment.

6. Systematic Literature Review on Nonthermal SWD

FDA conducted a systematic literature review to assess the safety and effectiveness of nonthermal SWD by analyzing the existing clinical literature from 1970 to the present. While this did exclude some pre-1970 references, FDA believed a search covering a 40-year span would capture the most relevant research; a significant majority of the references were published after 1970. In addition, FDA conducted the systematic literature review only for the cleared indications for use: adjunctive use in the palliative treatment of postoperative pain and edema in superficial soft tissue, and treatment of edema following blepharoplasty. While applications of nonthermal SWD for health conditions not yet cleared under 21 CFR 890.5290(b), as of January 2013, are present in the publications database, these indications for use, listed in Appendix 1, are outside the scope of this review.

The literature review sought to address the following questions:

1. What is the evidence for effectiveness of nonthermal SWD devices for the treatment of postoperative pain and edema and treatment of edema following blepharoplasty?

2. What are the reported adverse events associated with the use of nonthermal SWD devices for the treatment of postoperative pain and edema and treatment of edema following blepharoplasty? (see Section 4 for adverse events reported to FDA via the MAUDE database)

6.1. Methods

On January 12, 2013, FDA searched the published literature in PubMed using the following search terms:

- (27.12 MHz OR 27.12 megahertz) OR
- "pulsed electromagnetic device" OR
- "non-thermal pulsed electromagnetic energy" OR
- "pulsed electromagnetic energy" OR
- "pulsed electromagnetic" OR
- "Pulsed Radio Frequency Energy" OR
- "pulsed short wave diathermy" OR
- "short-wave diathermy" OR
- "short wave diathermy" OR
- "radio-frequency diathermy" OR
- "radiofrequency diathermy" OR
- "rf diathermy" OR
- "radio frequency diathermy" OR
- "radiofrequency exposure from therapeutic diathermy" OR
- "electromagnetic therapy" OR
- "shortwave therapy" OR
- ("radiofrequency exposure from therapeutic diathermy" NOT (deep heat) NOT (malignancy)

The search was limited to studies published after January 1, 1970, human studies, and those published in English. We permitted RCTs, observational studies, systematic literature reviews, meta-analyses, and case series with $n \geq 5$. The frequency of 27.12 MHz is included as it is the most widely used in clinical practice and generators in this frequency range are easier and less expensive to construct. This search yielded a total of 620 unique hits. A first pass of the articles was conducted by reviewing the title and abstract of each returned hit, excluding for: case reports, non-human studies, non-research articles, non-systematic reviews, and papers covering an unrelated device type or a non-approved indication for use (IFU).

Of the 620 identified articles, 317 were excluded in a round of exclusions by review of titles and abstracts. Titles were excluded during this time for the following reasons:

- case report (n =16);
- non-research article (n =1);
- non-human (n=140);
- non-systematic review (n =48);
- unrelated device type (n =34);
- unrelated indication(s) for use (IFU) (n =36); and
- non-study (n =42).

These exclusions left 303 articles for review during the second pass, for full epidemiological review and assessment.

During the second pass, 296 articles were excluded for the following reasons:

- case report (n =3);
- case series <5 (n =7);
- non-human (n =13);
- non-research article (n =27);
- non-systematic review (n =7);
- unrelated device type (n =180); and
- unrelated IFU (n =59).

At the end of the article selection process, 7 articles, listed in Table 3, were retained for full epidemiological analysis and data synthesis [9-15]. Additional information regarding the methodology for inclusion and exclusion criteria may be found in Figure 5.

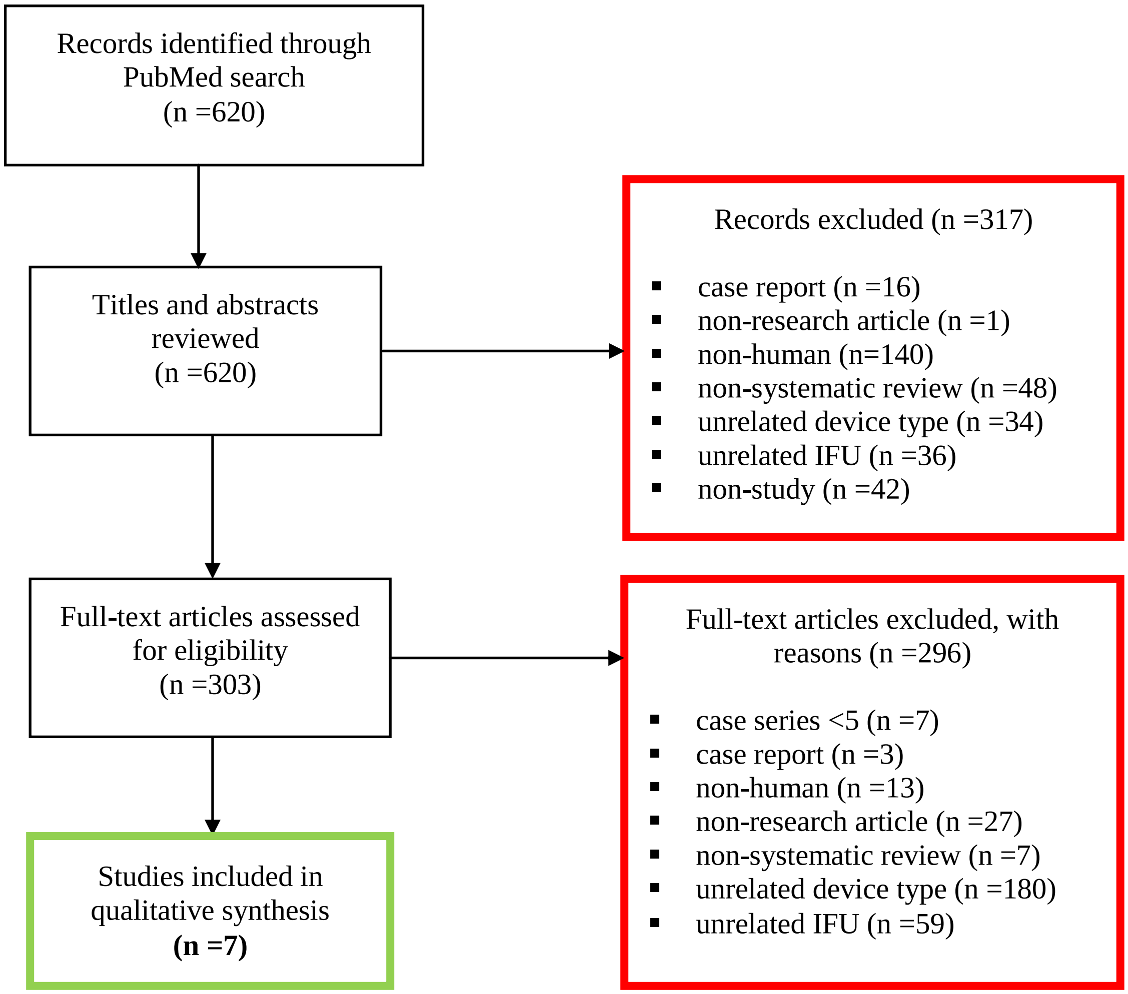

Figure 5 – Diagram of Article Retrieval and Selection

6.2. Summary of Results

A systematic literature review was conducted to evaluate the safety and effectiveness of nonthermal SWD for FDA-cleared on-label uses of postoperative pain, postoperative edema, and edema following blepharoplasty. Seven papers were identified in this systematic literature review, including 3 randomized controlled trials (RCTs), 3 observational studies, and 1 systematic literature review and meta-analysis (Table 4). These studies evaluated the effectiveness of nonthermal SWD on FDA-cleared indications in patients undergoing various procedures including oral, foot, breast augmentation, inguinal hernia repair, and plastic (eye) surgeries. These studies were published between 1978 and 2012. Among studies with primary data collection, sample size ranged from 21 to 82, with 4 of the 6 studies enrolling 50 participants or less. Of the 6 primary research studies, three were conducted in the United States, two in the United Kingdom, and one in Sweden. All 6 studies recruited patients from a single clinical site within these countries.

6.3. Study Designs and Methodology

The seven papers included in this systematic review varied in study design and methodology. A number of different nonthermal SWD devices were evaluated, including SofPulse [11], Magnatherm 1000 [15], Diapulse [12], ActiPatch [9], a proprietary device developed by Bental [13], and Therafield Beta Pulsed Electromagnetic Energy device [14]. It should be noted not all of these devices have a 510(k) cleared under 21 CFR 890.5290(b). A variety of different SWD devices were used in the individual studies included in the systematic review and meta-analysis by Guo et al. [10]. Although electrical parameters of the nonthermal SWD devices were consistent with definitions of nonthermal shortwave diathermy as defined by 21 CFR 890.5290(b), there was little standardization across studies for specific parameters of use, such as the duration and frequency of treatment sessions (Table 2).

Study endpoints included subjective measures of postoperative pain and edema. Pain was evaluated using the following instruments: 11-point scale (0 to 10) in which 0 represented no pain and 10 represented the worst pain ever experienced by the patient [9]; Visual Analog Scale (VAS) where "No Pain"= 0 mm and the "Worst Possible Pain"= 100 mm [11]; pain rating using a linear analog scale [14]; 4-point pain rating scale (none, mild, moderate, or severe) [12]; and postoperative pain medication use [11, 12, 14, 15]. Postoperative edema was rated on an 11-point percentage scale from 0 to 100, where patients were asked how much more or less swelling the right eye had compared to the left eye, with 0 representing identical amounts on both eyes [9]. The study by Nicolle et al. [13] did not specify how edema was evaluated [13]. Lastly, postoperative pain and edema were evaluated using various methods in the individual studies that were included in the literature review and meta-analysis by Guo et al. [10].

There were 4 papers that examined the pain indication only [11, 12, 14, 15], 1 paper that examined postoperative edema only [13], and 2 papers that examined both postoperative pain and edema [9, 10]. The main findings on the effectiveness and safety of nonthermal SWD on treatment of postoperative pain and edema are presented below.

6.4. Effectiveness Findings for Postoperative Pain

In our literature search, we identified 6 papers that examined the effect of nonthermal SWD on measures of postoperative pain (3 RCTs, 2 observational studies, and 1 systematic literature review and meta-analysis).

The three RCTs demonstrated divergent results for the postoperative pain indication. In the study by Hedén et al. [11] of 42 women undergoing breast augmentation, women who had both breasts treated with nonthermal SWD reported a lower mean VAS pain score on postoperative day 3 compared to women who had both breasts treated with a sham device (28.5±4mm vs. 40.2±3.5mm, $P<0.01$). In addition, a lower mean analgesic pill count was reported in the SWD-treated versus sham-treated women (3.1±0.3 vs. 4.9±0.5, P-value not reported)[11]. In contrast to these findings, Czyz et al. [9] reported no difference in pain on the 11-point pain scale (0 – 10) between the active nonthermal SWD treatment and sham control groups in a randomized control trial of 54 patients undergoing blepharoplasty (1.3±2.0 vs. 1.6±2.2, P=0.76). Reed et al. [14] reported similar negative findings in an RCT of 43 patients undergoing elective inguinal hernia repair. No difference in pain scores were observed between the nonthermal SWD and control groups at 24 hours (26.9±3.1 vs. 30.9±3.1, P>0.05) and at 48 hours (25.8±5.2 vs. 21.4±2.1, P>0.05) after surgery. In addition, there was no difference in the use of pain medications between the nonthermal SWD and control groups (P>0.05). Assessments of pain in the Reed et al. study were made by an independent observer using a "linear analog" scale. However, the use of the linear VAS through an independent observer is not a validated method for the assessment of postoperative pain.

Observational studies of postoperative pain also reported divergent findings. In the study by Santiesteban et al. [15] of 50 patients undergoing foot surgery, subjects treated with nonthermal SWD[5] reported a lower mean frequency of postoperative pain medications used compared to the control group (6.04 vs. 8.00, P<0.01). The use of analgesic medications was assessed using a non-validated scale. In contrast, Hutchinson et al. [12] reported no differences in pain rating and also pain medication use between the nonthermal SWD and control groups among 82 patients undergoing oral surgery (no statistics reported). Pain was rated by the subject into one of the following categories: no pain; mild pain, moderate pain, and severe pain.

Findings from the RCTs and observational studies described above need to be seen in light of considerable limitations in study design (Table 5). First, the studies had relatively small sample size, with 3 of the 6 studies enrolling 50 participants or less. Additionally, all were conducted at a single clinical site with the exception of the Reed et al. study [14] in which the number of participating study sites was not disclosed. The small sample size and single-site experience issues present a problem regarding representativeness of the study samples and, therefore, limit the generalizeability of these findings to surgical patients at large who are treated with nonthermal SWD for on-label use.

Second, pain was assessed by measures including an unvalidated use of a "linear analog scale" [14], and frequency of analgesic medication use after surgery [12, 14, 15]. Some validated measures were also used, including the VAS scale [11], 4-point pain rating scale (none, mild, moderate, severe pain) [12], and an 11-point scale (0 – 10) for pain [9]. There is a strong potential for a placebo effect in studies where the outcome of interest is largely assessed by patient-reported symptoms. Our review included studies with SWD-treated and control groups that reported comparable

[5] Patients were treated with Magnatherm 1000 device for 30 minutes as soon as possible after surgery and again 4 hours after the first application. The authors described this device as being nonthermal SWD; however, some treated patients reported a subjective feeling of mild heat. The skin after treatment was reported to be warm to the touch. The authors argue, "at the dosage used in this study, tissue heating may have been secondary in importance to other physiologic athermic processes."

levels of postoperative pain [9, 12, 14] and postoperative edema [9], suggesting either a placebo effect in the control group or ineffectiveness of nonthermal SWD in the active treatment group.

Third, the observational studies evaluating the devices and clinical outcomes had poorly defined patient selection criteria as well as limited reporting of data and methodology. While studies by Nicolle et al. [13] and Santiesteban et al. [15] reported improvements in postoperative outcomes, the lack of detailed reporting of other pain management and treatment modalities hinders the interpretation of the study results.

Lastly, many of the studies had inadequate statistical methods. For example, none of the studies performed any type of statistical adjustment for key confounders such as comorbidities that may alter pain perception. In addition, the observational study by Nicolle et al. [13] was largely descriptive and did not perform any statistical testing.

The systematic literature review and meta-analysis by Guo et al. also evaluated the effectiveness of nonthermal SWD for postoperative pain. This meta-analysis included 5 studies, all of which are described individually in Sections 6 and 7 of this document [11, 12, 16-18]. There were total of 350 SWD treated and 317 control patients, a reduction in postoperative pain was reported, with 4 of 5 studies demonstrating benefit of nonthermal SWD in reducing postoperative pain ($P<0.0001$)[10]. While these findings suggest a benefit of SWD treatment for postoperative pain, the study designs had notable limitations. A vote-counting procedure of assigning value to studies as positive, negative or neutral for nonthermal SWD effectiveness and a sum of logs method of p-value combination were used in this study, which are unproven methods in meta-analyses. Furthermore, the vote-counting procedure has an assumption that the combined studies are similar in study parameters for appropriate combination of results. However, the studies in the meta-analysis were heterogeneous in terms of sample size, patient populations, type of surgery and pain assessment, follow-up time and additional pain management modalities. As stated in the authors' section on statistical analyses, "an overall meta-analytic estimate of treatment effect would not be possible given the amount of heterogeneity observed." The meta-analyses also did not present formal statistical tests on the probability of unpublished studies due to negative study findings (e.g., Forest plots). Thus, interpretation of combination of the selected studies and the appropriateness of the combination remains unclear. Additionally, the sum of logs method of p-value provides information on the statistical significance of the summary statistics in the meta-analysis. However, clinical interpretation of effect of the nonthermal SWD on postoperative pain and edema should include the effect sizes measured.

6.5. Effectiveness Findings for Postoperative Edema

There were 3 studies that investigated the impact of nonthermal SWD on postoperative edema (1 RCT, 1 observational study, and 1 systematic literature review and meta-analysis).

In the RCT of 54 patients undergoing blepharoplasty who were blinded to nonthermal SWD treatment allocation, an average of 6% less edema was reported in the nonthermal SWD-treated eye compared to the eye treated with placebo (P=0.11) [9]. Similarly, the physician-graded edema had a non-significant mean Likert-type scale difference (assessment from -5 to +5) between the active and placebo treated eyes of -0.3 (P=0.12) [9]. Subjects were allowed to use local cooling with ice and reported using it for an average of 10-15 minutes 5 to 6 times per day.

The observational study by Nicolle et al. [13] described the experience of 21 patients undergoing bilateral blepharoplasty with and without nonthermal SWD treatment. Objective measurement scales were not used. In 6 subjects, postoperative edema was so minimal that no difference was visible between the treated and untreated eyes. Improvement was apparent in 11 subjects, with less edema noted on the treated versus untreated eye at 24 hours after the surgical procedure and this improvement persisted after 6 days. Lastly, in 2 subjects, postoperative edema was worse on the nonthermal SWD-treated (versus not treated) eye [13].

The systematic review and meta-analysis, which evaluated 5 studies for postoperative edema. These studies, which are described individually in Sections 6 and 7 of this document [12, 13, 16-18], had a total of 355 nonthermal SWD treated patients and 324 patients in the control group reported less edema in patients receiving active treatment compared to control (P<0.0001 by sum of logs method of p-value combination) [10].

6.6. Adverse Events Associated with Nonthermal SWD Use in the Palliative Treatment of Postoperative Pain and Edema and Treatment of Edema Following Blepharoplasty

We evaluated the safety of nonthermal SWD in the seven studies included in our systematic literature review. (See Section 4 for adverse events reported to FDA via MAUDE database.) No adverse events were reported in 3 of the 6 papers [10, 11, 13]. The study by Czyz et al. [9] reported unilateral postoperative hemorrhage on the SWD-treated eye in one patient that did not require any intervention. In addition, two patients experienced bilateral skin defects in the areas of patch placement on their temples due to improper application of nonthermal SWD device. In the Hutchinson et al. study of patients undergoing dental surgery [12], 5 dry sockets (3 SWD and 2 control) and 2 soft tissue infection requiring antibiotic therapy (1 SWD and 1 control) were reported. In addition, one man reported postoperative bleeding 24 hours after surgery that required packing and another man reported secondary bleeding on postoperative day 4. Both of these bleeding AEs occurred in the control group. Lastly, studies by Santiesteban et al. [15] and Reed et al. [14] did not report whether or not any adverse events occurred. It is important to note that, while only 2 of the 6 studies reported any complications, adverse events were not captured systematically in all 6 studies, and that may contribute to under-reporting of nonthermal SWD-related adverse events in the literature.

6.7. Overall Literature Review Conclusions

We searched over four decades of published scientific literature for studies evaluating the safety and effectiveness of nonthermal SWD for FDA-cleared indications of postoperative pain and edema in patients undergoing blepharoplasty and other surgical procedures. Our systematic search resulted in only 7 papers. Some of these studies reported a beneficial impact of nonthermal SWD on treatment of postoperative pain and edema while other studies demonstrated no effect. These mixed study findings need to be considered in light of key limitations in study design and methodology that limits the generalizability of the study results and may obscure the true effectiveness of nonthermal SWD for on-label use. Based solely on these findings, there does not appear to be sufficient evidence to reasonably demonstrate the safety and effectiveness of nonthermal SWD for postoperative pain and edema.

7. Additional Published Literature Review

We have reviewed the requests to change the classification of nonthermal SWD submitted to the docket in response to our proposed rule of July 6, 2012, and identified four studies in addition to the seven studies identified in our systematic literature review. These four studies include Kaplan at al. [17], Rohde et al. [18], and Rawe et al. [19], that are randomized prospective studies, and one study that is prospective but did not identify the method of assignment to one of three treatment groups (Aronofsky, [16]). The results of the four additional studies reviewed are summarized in Table **6**.

7.1. Review of Individual Studies

7.1.1. Randomized, Controlled Trials

Kaplan [17] conducted a prospective, randomized, and sham controlled study of postoperative pain and edema in 100 subjects following foot surgery. Subjects received treatment with the active or sham Diapulse device for 10 minutes within one hour prior to surgery and then twice per day until discharge, 15 minutes to the operative site and 15 minutes to the epigastrium at a slightly lower intensity. Assessments of pain intensity and edema were made by a blinded observer using a four point (none, trace, moderate, severe) scale. There were no significant reduction in pain or edema on postoperative days 1, 2 or 3 but statistically significant reductions of pain and edema were reported for the day of suture removal. The occurrence of adverse events was not addressed in this study.

Rohde et al. [18] conducted a prospective randomized sham controlled study of 24 subjects (12 per treatment arm) following breast reduction surgery. Subjects were treated for 20 minutes every 4 hours for the first 3 days; 15 minutes every 8 hours for the next 3 days and then every 12 hours to postoperative day 8. Analgesic use was standardized and monitored. Pain intensity was assessed using the 0 to 100 mm VAS. A statistically significant reduction in pain intensity was seen at 1, 5, 24, and 48 hours in the active treatment group compared to baseline and compared to the sham treated group. There was a significant reduction in the use of analgesics in the treatment group as well. This study also demonstrated a significant reduction in IL-1β levels in the drainage from the surgical site in the active treatment group compared to the sham treated group. No difference was seen for TNF-α, FGF-2 or VEGF. This study is limited by a small sample size but does provide limited support for the effectiveness of treatment for the condition studied. The device used is somewhat unique to the surgical procedure. It is not clear that the results would be applicable to the use of other devices for pain after other surgical procedures. It was reported that there were no adverse events, although there is no indication that adverse events were systematically collected.

Rawe et al. [19] conducted a prospective, double blind, sham controlled study of 18 patients following breast augmentation surgery. The sham device appeared to be identical to the active one. Treatment was continuous for 7 postoperative days. Pain was assessed by the subject using the 0-10 VAS scale twice a day. Analgesic use was collected. VAS scores were significantly lower for the active treatment group compared to sham for all days except postoperative day 2. Analgesic use was numerically lower in the active treatment group but the difference was not statistically significant (p-0.07). This study is limited by a very small sample size but does provide limited support for the effectiveness of the specific treatment method for pain following breast surgery. No adverse events were reported; however the systematic collection of adverse events was not clearly documented.

7.1.2. <u>Observational Study</u>

Aronofsky [16] studied pain following routine dental procedures. There is no indication that assignment was random. Two groups of 30 patients each received active treatment and the third group received no specified treatment. The methods of assessment of pain, specified endpoint and analysis methods are not described. The study reports statistically significant differences between the two treated groups and the untreated group. However, given the uncertainty regarding method of assignment to treatment groups, lack of use of validated assessment tools and lack of specified endpoints and analysis methods the results of this study are limited in terms of support for the effectiveness of treatment. The occurrence of adverse events was not addressed.

7.2. Summary of Additional Studies

There are a number of general design concerns in these four additional studies that are similar to the concerns regarding the studies captured in the systematic literature review. The exact primary endpoint and analysis methods are not clearly pre-specified in any of the studies. None of the publications included adequately detailed statistical analysis plans with pre-specified effectiveness and safety endpoints and planned adjustments for multiple analyses. Of the 4 studies, only 2 used validated scales for the assessment of pain intensity [14, 15]. The use of analgesic medications was assessed in the same 2 studies. None of the studies assessed the clinical relevance of any benefit demonstrated such as by reporting a responder rate (e.g., a 30% reduction in pain intensity) or patient/clinician global assessment of change score. Therefore, interpretation of any reported benefit for postoperative pain or edema is very limited for these four studies as is the case for the studies identified in the systematic literature review.

Note that the device output parameters vary among the studies. The devices used are shown in Table 2 along with the output parameters and treatment plans used.

8. Overall Clinical Review Conclusions

8.1. Study Design

There were 3 RCTs captured in the systematic review [9, 11, 14], and 3 additional RCTs [17-19] identified that studied postoperative pain and/or edema. FDA does not consider observational studies alone to be adequate to support the safety or effectiveness of treatments for pain or edema. Given the subjective nature of pain and edema assessments used in these studies, it is especially important that these trials include a concurrent placebo or sham comparator. Blinding of subjects and assessors in the RCTs was generally adequate, including the use of an appropriate sham device. However, all of the studies were single center studies and therefore, the results are not necessarily applicable to all potential prescribers or to all patients.

Three of the RCTs studied pain following breast surgery [11, 18, 19]; the benefit seen in these studies is not necessarily applicable to all procedures. The remaining 3 RCTs studied pain following other types of procedures: hernia repair [14], blepharoplasty [9], and foot surgery [17].

Four of the six studies used validated measures for pain [9, 11, 18, 19]; one did not [14, 17]; one was inadequately described [14]. Two of the six RCTs studied edema [9, 17]; neither of these used a validated measure of edema.

8.2. Method of Treatment

The parameters used in the available studies vary (Table 2). While two of the three RCTs for pain after breast surgery used the same device and comparable treatment regimens [11, 18], the third used a different device and a significantly different treatment regimen [19]. There is even wider variability in the methods used in the other three RCTs. Therefore, these studies provide no guidance as to which device settings (e.g., pulse sequences and intensities) may be effective or safe for the treatment of postoperative pain or edema.

8.3. Analysis Methods

None of the reports reviewed adequately document the pre-specified primary endpoint, analysis methods and appropriate adjustments for multiple analyses. Interpretation of claims of statistical significant benefit is therefore limited. Most studies did use a validated scale for pain intensity. None of the studies addressed the clinical relevance of any reported change in pain intensity. None used a responder definition or assessed the clinician or patient impression of improvement. Several did support clinical relevance by assessing the use of analgesic medications.

8.4. Effectiveness for Postoperative Pain

All three RCTs of pain following breast surgery [11, 18, 19] suggest a benefit for the use of a specific device for post-procedural pain. Two other RCTs showed no benefit for pain following blepharoplasty [9] or hernia repair [14]. The final RCT [17] did not show any benefit for post-surgical pain for the first 3 days after foot surgery, but did show benefit when patients returned for suture removal. The absence of benefit in the first 3 days makes the reported benefit at suture removal of questionable clinical relevance.

8.5. Effectiveness for Postoperative Edema

There are only two RCTs, which assessed postoperative edema [9, 17]. Neither study used a validated endpoint for edema. The RCT for patients undergoing blepharoplasty [9] did not show a statistically significant reduction of edema in the eye. The RCT for patients undergoing foot surgery [17], showed no benefit for edema in the first 3 days following surgery, but a statistically significant change of edema when patients returned for suture removal. The absence of benefit in the first 3 days makes the reported benefit at suture removal of questionable clinical relevance.

8.6. Safety

None of the literature references reviewed documented prospective and systematic collection of adverse events. The only adverse events of note were two “skin defects,” which occurred with the misuse of a low power nonthermal SWD device. These two events raise concerns for skin burns with misuse of these devices even at low power.

The small number of reports to the MAUDE database suggests the potential for minimal injury due to SWD (Section 4).

8.7. Overall Conclusion

The body of valid scientific evidence is limited and the results of the available studies are inconsistent. Major findings include the following:

- The data reviewed are not adequate to demonstrate a reasonable assurance of effectiveness of nonthermal SWD for the broad indication of postoperative pain or edema.

- There is evidence that randomized controlled trials of a specific device for pain following a specific procedure such as post-breast surgery pain are feasible and can demonstrate a clinically relevant benefit.

- The absence of a benefit in studies of pain following procedures other than breast surgery is consistent with the expectation that each device and each procedure represent a unique clinical situation for which effectiveness would have to be supported by clinical performance data.

- There are no commonly used or validated measures of postoperative edema.

- Although the clinical studies were not designed to systematically capture adverse event information, the limited safety data do suggest that even low power SWD devices may cause injury if not used properly. The available studies are not adequate to establish a reasonable assurance of safety of SWD for the cleared indications.

The panel will be asked to discuss whether special controls can provide reasonable assurance of device safety and effectiveness for nonthermal SWD for the indications for use of "adjunctive use in the palliative treatment of postoperative edema and pain" and "treatment of edema following blepharoplasty."

9. Summary

SWD devices are currently classified in Class III. In light of the information available now, the Panel will be asked to comment on whether SWD fulfills the statutory definition associated with a Class III device designation. FDA believes that these devices may be more appropriately regulated as:

- Class II, meaning general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness

As opposed to:

- Class III, meaning
    - insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

Nonthermal SWD is not life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health. However, whether these devices present a potential unreasonable risk of illness or injury is less clear, and previously, FDA recommended Class III for these devices based on this factor.

FDA is seeking the Panel's input regarding whether the available scientific evidence supports a Class III determination or a Class II determination with appropriate special controls, including the necessity of supportive clinical performance data.

For the purposes of classification, FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;

2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

4. The reliability of the device.

Part (g)(1) of this regulation further states that it "is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into Class III."

9.1. Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

In plain language, the definition states that a reasonable assurance of safety exists if, when using the device properly:

- The probable benefits to health outweigh the probable risks, and
- There is an absence of unreasonable risk of illness or injury

As the literature reviews demonstrate, nonthermal SWD is not without risk, although there has been limited adverse event information reported with the devices according to the Manufacturer and User facility Device Experience (MAUDE) database (see Section 4). While the events reported in the literature have generally not been serious, the lack of consistent reporting makes it difficult to draw conclusions about the safety of nonthermal SWD. The Panel should consider whether the risks to health can be mitigated through special controls or whether nonthermal SWD devices provide an unreasonable level of risks of injury that warrants the need for a Class III designation.

9.2. Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e)(1), "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

In plain language, the definition states that if using the device properly provides clinically significant results in a significant portion of the target population, there is a reasonable assurance of effectiveness.

Regarding the available literature, FDA has found that the effectiveness of nonthermal SWD has not been established by adequate scientific evidence for the cleared indications for use. The reviews that FDA has performed on the data have demonstrated that while there are several published literature on the use of nonthermal SWD for the treatment of postoperative pain and edema, most of the studies have limitations, such as small sample size, single site study, and different outcomes for the same intended use using the same device. These preclude favorable interpretations of the effectiveness results currently available.

Based on the literature discussed in this document coupled with the statutory definitions for a device to be designated as a Class III device, FDA will be seeking input on the appropriateness of including the requirement of clinical data as a special control to support a Class II recommendation. The Panel will be asked to comment on whether the available scientific evidence supports a Class III determination or a Class II determination with appropriate special controls, which may include supportive clinical data.

9.3. Special Controls

The comments to request a change in classification have proposed special controls (see Section 3.2) to be enacted in conjunction with reclassification. If the Panel were to recommend a Class II determination, FDA believes that the special controls proposed below should be included as part of the full list of special controls. FDA believes that clinical performance data are also needed to demonstrate device effectiveness. FDA proposes that special controls for nonthermal SWD devices would include the following. Exact language of the requirements would be based on panel feedback:

- Labeling – labeling must include adequate instructions for use, identification of indicated patient population, contraindications, and warnings about the possibility of unsafe use.

- Biocompatibility Testing – patient contacting materials must be evaluated and tested accordingly.

- Electrical Safety Testing – electrical safety testing must be provided to assure that the user is safe from unintended electrical energy deliver.

- Electromagnetic Compatibility and Interference (EMC/EMI) Testing – EMC/EMI testing must be provided to ensure that the nonthermal SWD device does not affect functionality of neighboring devices and that neighboring devices do not affect the nonthermal SWD device.

- Device Characterization and Non-Clinical Performance Testing – the output characteristics including the following must be characterized:
    - output power
    - pulse width
    - pulse frequency
    - duty cycle
    - average output powered measured from the applicator
    - specific absorption rates (SAR)
    - characterization of the electrical and magnetic fields for each RF antenna and RF antenna orientation/position
    - characterization of the deposited energy density

- Clinical Testing – clinical testing must demonstrate a reasonable assurance of safety and effectiveness. Studies should include the following basic study design elements:
    - Randomization
    - Sham control group

- Well-defined patient population, e.g. patients having a specific surgical procedure
- Well-defined SWD treatment parameters and device settings
- Clinically relevant validated measures of effectiveness
- Adequate power and sample size
- Appropriate statistical methods
- Predefined success criteria
- Systematic collection of adverse events

FDA believes clinical data are necessary for the following reasons:

- Existing literature do not conclusively demonstrate safety and effectiveness of the nonthermal SWD.

- The nonthermal SWD devices have a wide range of output parameters and treatment regimens (noted in Table 2) and the correlation with device performance is not clear.

- Given the subjective nature of the indications for use (postoperative pain & edema), there are not adequate animal models to be used in lieu of collection of clinical data.

FDA believes that clinical data are necessary to demonstrate reasonable assurance of effectiveness for all new devices.

The panel will be asked whether the proposed special controls can adequately mitigate the risks to health for nonthermal SWD devices and provide a reasonable assurance of safety and effectiveness in light of the available scientific evidence.

9.4. Reclassification

As previously noted, FDA considers a device Class II when general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness. However, a device will be considered Class III if

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

The literature search found no conclusive evidence of effectiveness. Some adverse events were noted in the literature and some are reported to FDA via MAUDE database. FDA is seeking the Panel's input regarding whether these devices present a potential unreasonable risk of illness or injury based on the available scientific evidence that warrants a Class III designation.

In order to change the classification of nonthermal SWD from Class III to Class II, FDA must have sufficient information to establish special controls that can provide reasonable assurance of the safety and effectiveness that, when using the device properly:

1. The probable benefits to health from using the device will outweigh the probable risks (per the definition of a reasonable assurance of safety, 21 CFR 860.7(d)(1))

2. There is an absence of unreasonable risk of illness or injury (per the definition of a reasonable assurance of safety)

3. The device will provide clinically significant results in a significant portion of the target population (per the definition of a reasonable assurance of effectiveness, 21 CFR 860.7(e)(1))

One device being Class II and another Class III depends on the availability of sufficient information to establish special controls, even though the risk profiles may be similar.

Special controls include "the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents (including guidance on the submission of clinical data in premarket notification submissions in accordance with section 510(k) of the act), recommendations, and other appropriate actions as the Commissioner deems necessary to provide such assurance."

To state that there is sufficient information to establish special controls to provide reasonable assurance of effectiveness implies two things:

1. The indications for use adequately define a target population.

2. The available evidence demonstrates that there are clinically significant results in a significant portion of that target population.

For nonthermal SWD devices, FDA believes that the available evidence suggests that special controls can be used to provide a reasonable assurance of safety and effectiveness. Special controls can be defined to address safety; for example, compliance with electrical safety standards, or adequate labeling. FDA also recommends that special controls include a requirement for clinical performance data to establish effectiveness for nonthermal SWD devices for specific output parameters and clinical conditions.

Based on the available scientific evidence and proposed special controls, the panel will be asked whether a Class III or Class II designation is appropriate for nonthermal SWD for the indications of "adjunctive use in the palliative treatment of postoperative pain and edema in superficial soft tissue" and "the treatment of edema following blepharoplasty."

10. Tables

Table 2 – Reported output parameters used in prospective studies of nonthermal SWD for postoperative pain and/or edema

Study	Device	Carrier frequency	Pulse frequency	Pulse duration	Peak power	Treatment duration
Hedén et al., 2008 [11]	SofPulse	27.12MHz	2 Hz	2 msec		30 min every 4h x 3d; q8h x 3d;q12 to day 8
Hutchinson et al., 1978 [12]	Diapulse	27.12MHz	500 Hz	65µsec	Setting of "5"	10 minute duration; just prior to and after surgery, then once/day for 3 days
Czyz et al., 2012 [9]	Actipatch	27.1MHz	1000 Hz			As tolerated for one week[1]
Nicolle, 1982 [13]	Non-commercial by Bental	27.12MHz	1000 Hz	100µsec	--	Not specified
Reed et al., 1987 [14]	Therafield Beta	27.12MHz	320 Hz	60µsec	1 Watt	Twice daily for 15min; duration not specified
Santiesteban, 1985 [15]	Magnatherm 1000,	27.12MHz	700 Hz	95µsec	"power setting of 12" or 120W	For 30 minutes after surgery; repeat at 4 hours. Patients reported mild heat and skin warm to touch after treatment.
Kaplan, 1968 [17]	Diapulse	27.12MHz	600 Hz	65µsec	975W	1 hr pre-op; post-op X2 treatments for 15 min
Aronofsky, 1971 [16]	Diapulse	27.12MHz	600 Hz	65µsec	975W	Group1: 24hr and 10min prior; 10min, 24, 48, 72 hr post-op Group 2: 10 min, 24, 48, 72 hr post-op
Rohde et al., 2010 [18]	SofPulse	27.12MHz	2 Hz	2 msec		20 min every 4h x 3d; q8h x 3d;q12 to day 8
Rawe et al., 2012 [19]	RecoveryRx	27.12MHz	1000 Hz	100µsec	0.0098W	Continuous

Back to Table of Contents

Table 3 – Publications included in the systematic literature review (n=7)

Author	Year	Study Design	Location
Guo L [10]	2012	Systematic literature review and meta-analysis	Various
Hedén P [11]	2008	RCT	Sweden
Hutchinson D [12]	1978	Observational Study	United Kingdom
Czyz CN [9]	2012	RCT	United States
Nicolle FV [13]	1982	Observational Study	United Kingdom
Reed M [14]	1987	RCT	United States
Santiesteban [15]	1985	Observational Study	United States

Back to Table of Contents

Table 4 – Descriptions of the Studies Evaluated in the Systematic Literature Review

Source [Author, Year]	Study Design Level of Evidence	Study Population	Sample Size	Devices Studied	Study Endpoints	Relevant Study Results [effect estimate and 95%CI]	Study Strengths and Limitations
Guo, L., 2012[10]	Systematic literature review and Meta-analysis	Patients undergoing various procedures including oral, foot, breast augmentation, and plastic (eye) surgeries	N=5 Pain Studies with 667 patients; Edema N=5 Edema Studies with 679 patients	Various pulsed radio frequency energy (PRFE) devices.	Postoperative pain and edema	5 of 6 studies reported lower levels of postoperative pain and edema in SWD-treated versus control-treated patients (P<0.001)	Strengths: a systematic search of the literature, pooling results from multiple clinical trials, 4 of 6 studies were RCTs; 3 of 6 studies were blinded Limitations: Heterogeneous in terms of patient population, SWD applications, pain measurement endpoints and follow-up time
Hedén, P., 2008[11]	Double-blind RCT	Women undergoing breast augmentation; conducted in	N=42	SofPulse^{TM}, Ivivi Technologies	Postoperative pain using Visual Analog Scale (VAS) where "No Pain"=0mm & "Worst Possible	On POD3, the bilateral SWD-treated group (compared to the bilateral control group) had a lower	Strengths: double-blind placebo-controlled RCT, validated pain measure; Limitations: Single

Source [Author, Year]	Study Design Level of Evidence	Study Population	Sample Size	Devices Studied	Study Endpoints	Relevant Study Results [effect estimate and 95%CI]	Study Strengths and Limitations
		Sweden			Pain"=100mm; And postoperative analgesic use	mean VAS pain score (28.5±4mm vs 40.2±3.5mm, P<0.01) and a lower mean analgesic pill count (3.1±0.3 vs. 4.9±0.5, P-value not reported). In the contralateral group, no difference in mean VAS score between SWD- and control-treated breasts on POD3 (29.3±3.8mm vs. 28.5±3.4mm, P=0.85). Mean pill count in the contralateral group was 3.2±0.4.	clinical site experience, small sample size
Hutchinson, D., 1978[12]	Observational Study	Healthy white men and women 18-30 y/o, undergoing removal of one mandibular third molar tooth under local anesthesia; conducted in UK	N=82 enrolled (74 analyzed)	Diapulse machine	Pain rating of (a) no pain, (b) mild pain, (c) moderate pain, (d) severe pain; Number of analgesic tablets (Paracetamol) taken after surgery	No difference in pain rating between Diapulse and control groups (no statistics reported)	Strengths: double-blinded, validated endpoint, relatively larger sample size; Limitations: Single clinical site experience of two oral surgeons, inadequate statistical methods
Czyz, C., 2012[9]	Double-blind RCT	Men and women undergoing blepharoplasty; Mean age 63±9 yrs (range: 43–80). Conducted in US	N=57 enrolled (54 analyzed)	ActiPatch, BioElectronics Corporation	11-point scale (0–10) for pain; Edema in R. vs. L. eyelids compared using 11-point scale (0–10), and rated on 11-point % scale from 0 -100. Surgeon	No difference in pain rating between eye treated with placebo patch vs. SWD patch (1.6±2.2 vs. 1.3±2.0, P=0.76). Pts reported a mean of 6 ± 30% (P=0.11) less edema in	Strengths: Utilized a placebo group; double-blind; validated measure for Pain Limitations: Device settings and time of use not fully quantified

Source [Author, Year]	Study Design Level of Evidence	Study Population	Sample Size	Devices Studied	Study Endpoints	Relevant Study Results [effect estimate and 95%CI]	Study Strengths and Limitations
					compared and rated edema based on an 11-point Likert-type scale (-5 to 5).	eye treated with SWD compared to placebo. Physician-graded edema had a mean Likert-type scale difference between placebo and SWD-treated eyes of -0.3±1.3 (P=0.12)	
Nicolle, F., 1982[13]	Observational Study	Consecutive blepharoplasty cases. Conducted in UK.	N=21enrolled (19 analyzed)	A proprietary device developed by Bental	Postoperative Edema – outcome measure not described in paper	In 6 cases, swelling was so slight that no difference was visible between SWD-treated and untreated eyes. In 11 cases, improvement was apparent with less edema on the SWD- vs. control-treated eye. 2 cases were worse on the SWD-treated eye.	Strengths: double-blind; Limitations: Small sample size; demographic information not captured; outcome measure not described, no statistical analysis performed.
Reed, M., 1987[14]	Double-blind RCT	Elective inguinal hernia repair; Conducted in US	N=43 (22 Sham; 21 SWD)	Therafield Beta PEME	Pain rating by linear analogue scale; analgesic consumption	No difference in pain scores between SWD and control groups at 24HRS postop (26.9±3.1 vs. 30.9±3.1, P>0.05) and at 48HRS postop (25.8±5.2 vs. 21.4±2.1, P>0.05); No difference in pain medication use between SWD and control groups (P>0.05 for all pain medications)	Strengths: Double-blind RCT Limitations: Small sample size; poor reproducibility of linear analogue scale pain assessment, unvalidated pain measure

Source [Author, Year]	Study Design Level of Evidence	Study Population	Sample Size	Devices Studied	Study Endpoints	Relevant Study Results [effect estimate and 95%CI]	Study Strengths and Limitations
Santiesteban A., 1985[15]	Observational Study	Patients undergoing foot surgery; age ranged from 24 to 72 yrs; conducted in US	N=50 (25 SWD and 25 Control)	Magnatherm 1000, International Medical	Frequency of analgesic medications taken	SWD group had a lower mean frequency of pain medications used compared to the No SWD (control) group (6.04 vs 8.00, P<0.01)	Strengths: Presence of a control group (although TX allocation was not random); Limitations: small sample size; unvalidated pain measure; all surgeries performed by 1 surgeon at single site; the control treatment was not described

Back to Table of Contents

Table 5 – Study Design Characteristics of the Six Primary Research Papers included in the Systematic Literature Review and the Four Additional Publications Evaluated

Author, Year	Study Design	Control Group	Masking	Sample Size ≥50	Multiple Sites	Validated Outcome Measure	Pre-Specified Hypothesis	Pre-Specified Endpoint for Success	Statistical Adjustment
Heden, 2008	RCT	X	X			X			
Reed, 1987	RCT	X	X		†				
Santiesteban, 1985	OBS	X		X					
Hutchinson, 1978	OBS	X	X	X		X			
Czyz, 2012	RCT	X	X	X		X*			
Nicolle, 1982	OBS	X	X						
Kaplan, 1968	RCT	X	X						
Aronofsky, 1971	OBS	X		X					
Rohde, 2010	RCT	X	X			X			
Rawe, 2012	RCT	X	X			X			

(X) indicates presence of the study design characteristic
* Validated outcome measure for pain but not edema
† Reed et al. did not report the number of clinical sites included in their study.

Back to Table of Contents

Table 6 – Description of the Additional Publications Evaluated

Source [Author, Year]	Study Design Level of Evidence	Study Population	Sample Size	Devices Studied	Study Endpoints	Relevant Study Results [effect estimate and 95%CI]	Study Strengths and Limitations
Kaplan, E., 1968 [17]	Double blind RCT.	Patients undergoing foot surgery	100	Diapulse	Postoperative pain and edema	No benefit for pain or edema days 1-3; statistically significant reduction in pain (p<.01) and edema (p<.01) on day of suture removal	Strengths: Double-blind sham controlled RCT Limitations: Lack of validated measures for pain and edema. Single center
Aronofsky, D., 1971 [16]	Observational	Routine dental procedures	90	Diapulse	Postoperative pain at 72 hours	Statistically significant reduction in pain at 72 hours post-procedure	Strengths: comparator group Limitations: Not randomized. Comparator not concurrent. Lack of validated scale for pain. Single center
Rohde, C., 2010 [18]	Double-blind RCT	Breast reduction surgery	24	SofPulse	Postoperative pain	Statistically significant reduction in postoperative pain at 1 hour (p<.01), 24 hours (p<.01 and 48 hours (p<.001) and pain medication use at 48 hours (p<.002) compared to sham.	Strengths: Double-blind sham controlled RCT. Validated pain scale. Narcotic equivalents measured. Limitations: small single center study.
Rawe,I., 2012 [19]	Double-blind RCT	Breast augmentation surgery	18	RecoveryRx	Postoperative pain	Statistically significant pain reduction on postoperative day 1 (p<0.017) and day 3 (p=0.003) and for all 7 postoperative days except day 2 (p=0.23). Pain medication use significantly reduced if one outlier removed.	Strengths: Double-blind sham controlled RCT. Validated pain scale. Analgesic use assessed. Limitations: small single center study.

Back to Table of Contents

11. References

1. Guy, A.W., J.F. Lehmann, and J.B. Stonebridge, *Therapeutic applications of electromagnetic power.* Proceedings of the IEEE, 1974. **62**(1): p. 55-75.
2. *48 Fed. Reg. 53042 (1983), Wednesday, November 23, 1983, page 53042*.
3. *IEEE Standard for Safety Levels With Respect to Human Exposure to Radio Frequency Electromagnetic Fields, 3 kHz to 300 GHz.* IEEE Std C95.1-2005 (Revision of IEEE Std C95.1-1991), 2006: p. 0_1-238.
4. International Commission on Non-Ionizing Radiation, P., *ICNIRP Guidelines For Limiting Exposure To Time-Varying Electric, Magnetic And Electromagnetic Fields (Up To 300 GHz)* Health Physics 1998. **74**(4): p. 494-522.
5. Dworkin, R.H., J. Katz, and M.J. Gitlin, *Placebo response in clinical trials of depression and its implications for research on chronic neuropathic pain.* Neurology, 2005. **65**(12 Suppl 4): p. S7-19.
6. Moore, R.A., et al., *Minimum efficacy criteria for comparisons between treatments using individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction.* Pain, 2011. **152**(5): p. 982-9.
7. Dworkin, R.H., et al., *Core outcome measures for chronic pain clinical trials: IMMPACT recommendations.* Pain, 2005. **113**(1-2): p. 9-19.
8. Dworkin, R.H., et al., *Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations.* J Pain, 2008. **9**(2): p. 105-21.
9. Czyz, C.N., et al., *Efficacy of pulsed electromagnetic energy in postoperative recovery from blepharoplasty.* Dermatol Surg, 2012. **38**(3): p. 445-50.
10. Guo, L., et al., *Meta-analysis of clinical efficacy of pulsed radio frequency energy treatment.* Ann Surg, 2012. **255**(3): p. 457-67.
11. Hedén, P. and A.A. Pilla, *Effects of pulsed electromagnetic fields on postoperative pain: a double-blind randomized pilot study in breast augmentation patients.* Aesthetic Plast Surg, 2008. **32**(4): p. 660-6.
12. Hutchinson, D., S. Witt, and C.G. Fairpo, *Pulsed electromagnetic energy therapy in third molar surgery.* Oral Surg Oral Med Oral Pathol, 1978. **46**(6): p. 748-54.
13. Nicolle, F.V. and R.M. Bentall, *Use of radio-frequency pulsed energy in the control of postoperative reaction in blepharoplasty.* Aesthetic Plast Surg, 1982. **6**(3): p. 169-71.
14. Reed, M.W., et al., *Pain relief after inguinal herniorrhaphy. Ineffectiveness of pulsed electromagnetic energy.* Br J Clin Pract, 1987. **41**(6): p. 782-4.
15. Santiesteban, A.J. and C. Grant, *Post-surgical effect of pulsed shortwave therapy.* J Am Podiatr Med Assoc, 1985. **75**(6): p. 306-9.
16. Aronofsky, D.H., *Reduction of dental postsurgical symptoms using nonthermal pulsed high-peak-power electromagnetic energy.* Oral Surg Oral Med Oral Pathol, 1971. **32**(5): p. 688-96.
17. Kaplan, E.G. and R.E. Weinstock, *Clinical evaluation of diapulse as adjunctive therapy following foot surgery.* J Am Podiatry Assoc, 1968. **58**(5): p. 218-21.
18. Rohde, C., et al., *Effects of pulsed electromagnetic fields on interleukin-1 beta and postoperative pain: a double-blind, placebo-controlled, pilot study in breast reduction patients.* Plast Reconstr Surg, 2010. **125**(6): p. 1620-9.

19. Rawe, I.M., et al., *Control of postoperative pain with a wearable continuously operating pulsed radiofrequency energy device: a preliminary study.* Aesthetic Plast Surg, 2012. **36**(2): p. 458-63.

[5-19]

Back to Table of Contents

12. Appendices

12.1. Appendix 1

The following includes a list of indications for use that are outside the scope of the literature review presented in this executive summary as nonthermal SWD devices have not been cleared for these indications:

- Acute tibial shaft fractures
- Stimulation of fibronectin synthesis
- Postoperative ileus
- Ununited fractures and arthrodesis
- Arthroscopic reconstruction of anterior cruciate ligament
- Posterolateral lumbar fusion
- Pseudoarthrosis of tibia hip revision prostheses
- Hair removal
- Venous stasis ULCERSs
- Cervical fusion
- Tinnitus treatment
- Perineal trauma
- Pelvic pain
- Acute scaphoid fractures
- Loosened cemented hip prostheses
- Acne vulgaris
- Multiple sclerosis fatigue
- Recalcitrant plantar fasciitis
- Ankle sprains
- Chronic low back pain
- Diabetic polyneuropathy
- Knee osteoarthritis
- Herpes zoster
- Plantar heel pain
- Benign prostatic hyperplasia
- Neck pain
- Dry eye syndrome
- Chronic pelvic inflammatory disease pain

Back to Table of Contents